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10/579,912	02/15/2007	Junji Nishigaki	2870-0335PUS1	6900

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
05/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/579,912	NISHIGAKI, JUNJI	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/19/2006, 7/31/2006, 8/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-8 are pending and are examined herein on the merits for patentability.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwendener (*J. Liposome Research*, 1994, 4(2), p. 837-855).

Schwendener discloses small unilamellar liposome preparations used as carriers for chelates of gadolinium as organ specific magnetic resonance imaging (MRI) contrast agents. The lipophilic membrane associated chelate DTPA-stearylamide (DTPA-SA) was investigated (abstract). Liposomes have gained interest as carriers for MRI contrast agents, mainly because of their natural targeting capability to the organs of the mononuclear phagocyte system (MPS), the liver and spleen. The liposomal preparations of lipophilic DTPA-SA were prepared as MPS specific contrast agents. Furthermore, liposomes modified with PE-PEG(5000) as carriers for Gd-BOPTA with potential for imaging of the vascular system are disclosed (page 839). The liposome components included soy phosphatidylcholine, cholesterol and D,L-alpha-tocopherol

(page 845). With regard to claims 6-8, imaging of lesions is disclosed, for example a strong contrast is expected between normal and pathological tissues. In addition, the preparations are MPS organ specific E.g. liver, spleen (page 851).

Claims 1,2, and 5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Glogard *et al.* (*International Journal of Pharmaceutics*, 2002, 233, p. 131-140).

Glogard discloses the effects of membrane composition (phospholipid type and amount of cholesterol), liposome size, drug/lipid ratio (loading) and nature of amphiphilic gadolinium (Gd) chelate on the incorporation efficacy and magnetic resonance (MR) contrast efficacy (longitudinal (T_1) relaxivity). A highly lipophilic Gd-chelate was required to ensure complete liposome incorporation (abstract). See Figure 1, incorporating Gd-HDD-DO3A or Gd-HHD-DO3A into a liposome system exemplified with DMPC/DMPG and cholesterol (page 133, right column). The incorporation of amphiphilic Gd-chelates into the liposomal membrane markedly enhanced the T_1-relaxivity (page 139, right column). With regard to claims 6-8, which recites that the MRI contrast medium is "used for imaging of a tissue or lesion where macrophages localize," it is noted that the recitation of the intended use of the composition has not been given patentable weight to distinguish over Glogard because the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Since Glogard discloses compositions having the same structural features as those claimed, they would be capable of performing the claimed intended use.

Claims 1, 2 and 5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Unger *et al.* (US 5,312,617).

Unger discloses novel complexes of paramagnetic ions and compounds bearing long acyl chains for use as magnetic resonance imaging contrast agents. The liposoluble contrast agents may be administered with lipids, in the form of liposomes, micelles or lipid emulsions, and have particular use in MRI imaging of the liver, blood pool and reticuloendothelial system (abstract). See Examples 1 and 8, in which Mn-EDTA-ODP, Mn-DTPA-OA-MEA, Gd-DTPA-ODP, Mn-EDTA-DDP and Md-EDTA-DDP are incorporated into small unilamellar liposomes including egg phosphatidylcholine (EPC) and cholesterol (8:2 molar ratio). The invention is useful in imaging a patient generally, and/or in specifically diagnosing the presence of diseased tissue in a patient. The imaging process may be carried out by administering a contrast medium of the invention to a patient, and then scanning the patient using magnetic resonance imaging to obtain visible images of an internal region of a patient and/or of any diseased tissue in that region. The contrast medium is particularly useful in providing images of the blood pool, liver, reticuloendothelial system, spleen, bone marrow, lymph nodes, and muscle. Also, as shown by their in vivo effectiveness at low doses, these agents are highly effective at enhancing the liver and highly useful for improving the detection of hepatic metastases (column 13, lines 1-20).

Claims 1, 2 and 5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Grant *et al.* (*Mag. Reson. Med.*, 1989, 11(2), p. 236-43 (abstract)).

Grant discloses that the chelating agent, diethylenetriaminepentaacetic acid (DTPA), was attached via one -COOH group to the amino headgroup of phosphatidylethanolamine to produce a phospholipid which is also a powerful chelating agent. It readily assembles into the walls of lipid bilayer structures as a liposome-associated carrier of cations for MR contrast or radioisotope studies. Freeze-etch electron microscopy showed that phosphatidylethanolamine-DTPA formed satisfactory sonicated vesicles when mixed with natural phospholipids at up to 50 wt%. The resultant structures with bound gadolinium effectively shortened T_1 and T_2 of surrounding water protons. When sonicated liposomes bearing chelating agent with bound 111In3+ were injected intravenously into rats, uptake was primarily by liver and spleen. By 24 h postinjection there was biliary excretion of this material. Phosphatidylethanolamine-DTPA may have some general utility as an amphiphilic liposomal chelating agent for polyvalent cations (abstract). With regard to claims 6-8, which recites that the MRI contrast medium is "used for imaging of a tissue or lesion where macrophages localize," it is noted that the compositions of Grant localize in liver. The recitation of the intended use of the composition has not been given patentable weight to distinguish over Grant because the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art

structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Since Grant discloses compositions having the same structural features as those claimed, they would be capable of performing the claimed intended use.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger *et al.* (US 5,312,617) in view of Takahashi *et al.* (WO 03/018530, whereby US 2005/0002864 is relied upon for translation).

Unger discloses novel complexes of paramagnetic ions and compounds bearing long acyl chains for use as magnetic resonance imaging contrast agents. The

liposoluble contrast agents may be administered with lipids, in the form of liposomes, micelles or lipid emulsions, and have particular use in MRI imaging of the liver, blood pool and reticuloendothelial system (abstract). See Examples 1 and 8, in which Mn-EDTA-ODP, Mn-DTPA-OA-MEA, Gd-DTPA-ODP, Mn-EDTA-DDP and Md-EDTA-DDP are incorporated into small unilamellar liposomes including egg phosphatidylcholine (EPC) and cholesterol (8:2 molar ratio). The invention is useful in imaging a patient generally, and/or in specifically diagnosing the presence of diseased tissue in a patient. The imaging process may be carried out by administering a contrast medium of the invention to a patient, and then scanning the patient using magnetic resonance imaging to obtain visible images of an internal region of a patient and/or of any diseased tissue in that region. The contrast medium is particularly useful in providing images of the blood pool, liver, reticuloendothelial system, spleen, bone marrow, lymph nodes, and muscle. Also, as shown by their in vivo effectiveness at low doses, these agents are highly effective at enhancing the liver and highly useful for improving the detection of hepatic metastases (column 13, lines 1-20).

The liposoluble contrast agents may comprise a lipid, including cholesterols, phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, etc, and combinations thereof. As those skilled in the art will recognize, the lipids may be selected to optimize the particular diagnostic use, minimize toxicity and maximize shelf-life of the product. For example, neutral vesicles composed of phosphatidylcholine and cholesterol function quite well as intravascular contrast agents. To improve uptake by cells such as the reticuloendothelial system (RES), a negatively charged lipid such as

phosphatidylglycerol or phosphatidylserine may be added. The lipid compound employed may be in the form of a lipid emulsion, liposome or micelles, including methods of preparation that are well known in the art. The contrast agent is incorporated into the liposome membrane (column 9, lines 50 - column 11, line 27).

While Unger teaches that lipid combinations may be employed in liposome formulation, Unger does not specifically recite a molar ratio of phosphatidylcholine/phosphatidylserine used in liposome formulation.

Takahashi teaches liposoluble 1,3-diacylglyceride compounds having two iodophenyl groups used as a liposome membrane component and a contrast agent for x-ray radiography (paragraph 0001, 0008). The liposome preferably contains a combination of phosphatidylserine and phosphatidylcholine as membrane components. The compositions are used as contrast media for x-ray radiography of tissue or a lesion in which macrophages localize selected from liver, spleen, air vessel, lymph node, etc. and lesions selected from tumor, inflammation and infection (paragraph 0012). Any liposomes ordinarily used for preparation of liposomes can be used, preferably a combination of phosphatidylcholine and phosphatidylserine, preferably in the molar ratio of 90:10 to 10:90, further preferably in the range of 30:70 to 70:30 (paragraph 0031-0032). It is known that liposomes containing PC and PS are likely to accumulate on macrophages with the aid of scavenger receptors. Therefore, by using the liposomes of the present invention, the iodine compound can be accumulated in a tissue or lesion in which macrophages localize (paragraph 040). See also Table 1 for liposome formulations including 50 nmol PC + 50 nmol PS.

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the liposoluble contrast agents of Unger in a liposome comprising phosphatidylcholine and phosphatidylserine as lipid components. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Unger teaches that combinations of lipids can be used in liposome formulation, including cholesterol, phosphatidylcholine, phosphatidylserine, etc, and teaches the benefit of incorporating phosphatidylserine, which is to improve uptake by cells such as the reticuloendothelial system. With regard to the ratio of lipids employed in the formulation, Unger teaches that liposomes may be prepared according to methods known in the art, and also teaches that his formulations are preferably used to target liver, spleen, etc. One of ordinary skill would have been motivated to select liposomal ratios known in the art in order to provide the desired targeting, and would have recognized that PS:PC liposomes having molar ratio 3:7 to 7:3, such as 1:1 for example, would be useful for promoting accumulation in macrophages and targeting liver, as shown by Takahashi.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger *et al.* (US 5,312,617) in view of Gabizon *et al.* (Cancer Res., 1983, 43, 4730-4735).

Unger discloses novel complexes of paramagnetic ions and compounds bearing long acyl chains for use as magnetic resonance imaging contrast agents. The liposoluble contrast agents may be administered with lipids, in the form of liposomes,

micelles or lipid emulsions, and have particular use in MRI imaging of the liver, blood pool and reticuloendothelial system (abstract). See Examples 1 and 8, in which Mn-EDTA-ODP, Mn-DTPA-OA-MEA, Gd-DTPA-ODP, Mn-EDTA-DDP and Md-EDTA-DDP are incorporated into small unilamellar liposomes including egg phosphatidylcholine (EPC) and cholesterol (8:2 molar ratio). The invention is useful in imaging a patient generally, and/or in specifically diagnosing the presence of diseased tissue in a patient. The imaging process may be carried out by administering a contrast medium of the invention to a patient, and then scanning the patient using magnetic resonance imaging to obtain visible images of an internal region of a patient and/or of any diseased tissue in that region. The contrast medium is particularly useful in providing images of the blood pool, liver, reticuloendothelial system, spleen, bone marrow, lymph nodes, and muscle. Also, as shown by their in vivo effectiveness at low doses, these agents are highly effective at enhancing the liver and highly useful for improving the detection of hepatic metastases (column 13, lines 1-20).

The liposoluble contrast agents may comprise a lipid, including cholesterols, phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, etc, and combinations thereof. As those skilled in the art will recognize, the lipids may be selected to optimize the particular diagnostic use, minimize toxicity and maximize shelf-life of the product. For example, neutral vesicles composed of phosphatidylcholine and cholesterol function quite well as intravascular contrast agents. To improve uptake by cells such as the reticuloendothelial system (RES), a negatively charged lipid such as phosphatidylglycerol or phosphatidylserine may be added. The lipid compound

employed may be in the form of a lipid emulsion, liposome or micelles, including methods of preparation that are well known in the art. The contrast agent is incorporated into the liposome membrane (column 9, lines 50 - column 11, line 27).

While Unger teaches that lipid combinations may be employed in liposome formulation, Unger does not specifically recite a molar ratio of phosphatidylcholine/phosphatidylserine used in liposome formulation.

Gabizon teaches tissue distribution of liposome-entrapped Adriamycin (ADM) in mice with metastatic spread to the liver and spleen after inoculation of J-6456 lymphoma cells. Sonicated phosphatidylserine:phosphatidylcholine:cholesterol liposomes were used as carriers of ADM, based on previous studies on the drug entrapment, stability, and tissue distribution of ADM-containing liposomes of various compositions (abstract). Chromatographically pure egg PC, CHOL and bovine PS were purchased and the lipids were mixed according to the following molar ratio: PS, 3; PC, 7; and CHOL, 10 (page 4731 , left column). The ability of small sonicated liposomes to deliver increased amounts of ADM into J-6456 metastatic cells within the hepatic parenchyma, causing an enhanced killing of the tumor cells. Concomitantly, these liposomes were able to reduce significantly the cardiac uptake of ADM in tumor-bearing mice. Liposomes composed of PS:PC:CHOL (molar ratio 3:7:10) were chosen for this study based on previous investigations showing their high efficiency of drug entrapment and their ability to retain the drug in the presence of serum (page 4733, right column).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the liposoluble contrast agents of Unger in a liposome comprising

phosphatidylcholine and phosphatidylserine as lipid components. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Unger teaches that combinations of lipids can be used in liposome formulation, including cholesterol, phosphatidylcholine, phosphatidylserine, etc, and teaches the benefit of incorporating phosphatidylserine, which is to improve uptake by cells such as the reticuloendothelial system. With regard to the ratio of lipids employed in the formulation, Unger teaches that liposomes may be prepared according to methods known in the art, and also teaches that his formulations are preferably used to target liver, spleen, etc. One of ordinary skill would have been motivated to select liposomal ratios known in the art in order to provide the desired targeting, and would have recognized that PS:PC:CHOL liposomes having molar ratio 3:7:10 would be useful for targeting liver, as shown by Gabizon.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-24 of copending Application No. 11/635,641 in view of Grant *et al.* (*Mag. Reson. Med.*, 1989, 11(2), p. 236-43 (abstract)). The instant claims are drawn to a liposome containing a hydrophobic chelate compound as a membrane component. The claims of the '641 application are drawn to compounds of formula 1, including a liposome containing a compound of formula 1 as a membrane component. Both applications include liposomes containing phosphatidylserine and phosphatidylcholine as membrane components. While the instant claims are generic to the type of hydrophobic chelate

compound that is incorporated as a membrane component, it would have been obvious to use a compound of formula 1 from the '641 application as the hydrophobic chelate compound, when the claims are taken in view of Grant. Grant teaches that phosphatidylethanolamine-DTPA is a chelating agent in which DTPA is attached via one –COOH group to the amino head group of phosphatidylethanolamine (which meets the structure of formula 1 of the '641 application) to produce a phospholipid which readily assembles into the walls of lipid bilayer structures such as liposomes as a carrier for MR contrast agents or radioisotope studies. Since phosphatidylethanolamine-DTPA is a known hydrophobic chelate for incorporation into liposome, it would have been obvious to one of ordinary skill in the art to select it for incorporation into the instant claims for use as an MRI contrast agent. This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS